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Gerstmann-Straussler-Scheinker Disease With F198S Mutation Diagnosis on Repeat Genetic Testing: A Case Report

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Abstract

Gerstmann-Straussler-Scheinker (GSS) disease is a rare hereditary autosomal dominant prion disease characterized by cerebellar ataxia, dysarthria, and progressive dementia. We report a case of GSS disease in a 46-year-old patient who presented with four to six months of ataxia, dysarthria, intermittent tongue biting, and frontal headaches. His DaTscan (dopamine transporter scan) showed absent dopamine uptake in the left putamen and mildly decreased activity in the right putamen, a finding that has only been documented in the literature one other time for this GSS variant. Family history included the death of his father at age 58 from presumed multiple system atrophy (MSA). His symptoms and family history of parkinsonism prompted genetic testing, which revealed a F198S variant in the prion protein gene (PRNP), confirming a diagnosis of GSS disease.

Categories: Neurology, Genetics
Keywords: cerebellar ataxia, genetic testing, gerstmann-straussler-scheinker disease, movement disorder, prion disease

Introduction

Gerstmann-Straussler-Scheinker (GSS) disease is a rare hereditary autosomal dominant prion disease characterized initially by truncal ataxia, dysarthria, dysesthesia, and lower extremity hyporeflexia. Patients later develop progressive dementia, parkinsonism with limited response to levodopa, myoclonus, spasticity, and akinetic mutism, with symptom onset occurring from the third to sixth decade [1]. GSS is caused by pathogenic variants in the PRNP gene, most commonly P102L. Although more than 20 variants have been described, most cases present with ataxia followed by dementia at varying stages [2]. A large Indiana kindred is associated with the F198S variant [3]. The disease involves tau amyloid deposition in the cerebral cortex, basal ganglia, and cerebellum, interfering with dopaminergic transport and contributing to the presenting symptoms [4-6]. Management is supportive, including physical and speech therapy, as no disease-modifying treatment is available [7].

This case underscores the need to revisit genetic evaluation in patients with a strong family history of similar symptoms who present with an atypical parkinsonian phenotype. If earlier testing was negative, repeat genetic analysis using an alternative laboratory may be indicated.

Case Presentation

We report a case of GSS disease in a 46-year-old man with a past medical history of hypertension, familial hypertriglyceridemia, and gastroesophageal reflux disease (GERD), presenting with ataxia, dysarthria, intermittent tongue biting, and frontal headaches for four to six months. The patient did not have any history of previous meningitis or encephalitis diagnosis. The patient has several family members who were affected by memory problems and ataxia (Figure *1*) and who all passed away before the age of 60. His father died at age 58 from presumed multiple system atrophy (MSA) in 2006, prior to availability of genetic testing. His father presented similarly to the patient, also with ataxia and "clumsiness" as his presenting symptom, later progressing to develop dementia. His symptoms were not responsive to levodopa. He does not have any known family connection to the Indiana Kindred. Given his presentation, together with the strong family history of early-onset neurologic decline, there was concern for an inherited disorder.

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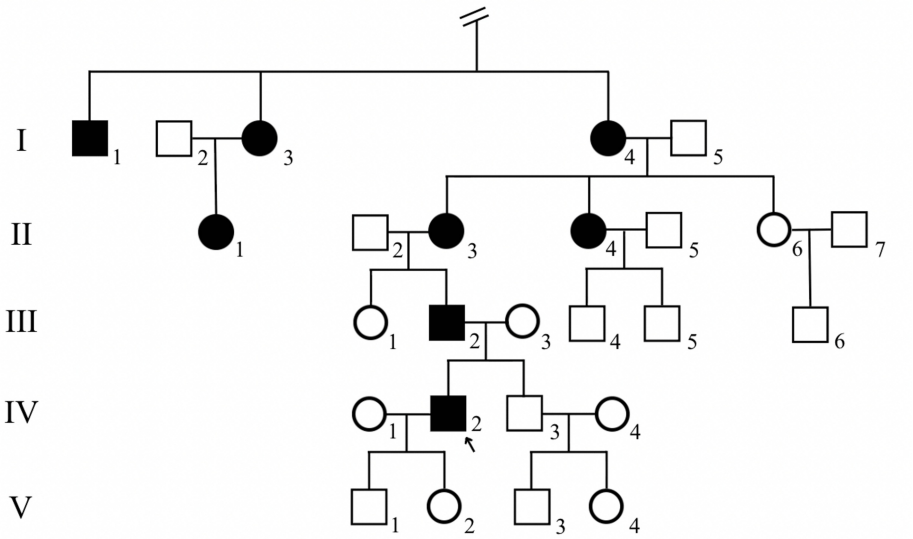


FIGURE 1: Family pedigree highlighting the autosomal dominant inheritance pattern. The arrow indicates the proband, a 46-year-old male diagnosed with GSS.

On the mental status exam, his Glasgow Coma Scale was 15, and he was awake, alert, and oriented to person, place, time, and event. He exhibited a normal mood and affect and normal memory and language. He did not demonstrate any hemineglect, but did have mild dysarthria. Cranial nerve exam demonstrated unremarkable fundi, pupils equal, round, and reactive to light. His visual acuity was grossly intact, and his visual fields were full to finger counting by confrontation. Extraocular movements were intact without nystagmus, and there was an absence of ptosis. Sensation to the face was symmetric to light touch in V1-V3. He demonstrated a symmetric smile and tight eye closure. His hearing was intact to finger rub bilaterally. His uvula and palate rise were midline. His shoulder shrug and head turn were symmetric with full strength. His tongue was midline on protrusion. His dizziness was not reproducible with head turning movements while sitting down. His muscle tone and bulk were normal, with no contractures or abnormal or involuntary movements. He demonstrated full strength except for bilateral plantarflexion weakness, in which he could plantarflex both feet against gravity but not with any resistance. Biceps, brachioradialis, triceps, patellar, and Achilles reflexes were full and symmetric without any clonus. Hoffman reflex was negative, and Babinski was downgoing bilaterally. He demonstrated mild dysmetria and ataxia, dysdiadochokinesia, equivocal finger-to-nose testing, and positive Romberg sign. His gait was cautious, and he was unable to walk on heels or toes due to a fear of falling over. His initial score on the scale for the assessment and rating of ataxia (SARA) was 11.5, with two points for speech, one point for nose-finger testing, 2.5 points for rapid alternating movement, two points for heel-to-shin testing, one point for ataxia while standing, and three points for ataxia while walking. His most recent SARA score was 24, with most significant worsening of ataxia on standing and walking [8].

MRI brain at the initial presentation was negative for acute infarction, bleeding, or intracranial mass, but did show mild cerebellar atrophy (Figure *2*). CSF cell count and glucose were within normal limits, and CSF protein was 45. Syn-One biopsy testing was recommended but was not covered by the patient's insurance and thus not ultimately done. Initial genetic testing with Athena in 2023 included the comprehensive ataxia evaluation, which tested for ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7, TBP, ATXN8OS, ATXN10, PPP2R2B, ATN1, AFG3L2, KCNC3, PRKCG, SPTBN2, EEF2, FGF14, ITPR1, KCND3, PDYN, TGM6, TTBK2, VAMP1, KCNA1, CACNB4, SLC1A3, CACNA1A, FXN, APTX, ATM, SETX, TTPA, ADCK3, AFG3L2, ANO10, FLVCR1, GRM1, MRE11A, MTPAP, SACS, SYNE1, SYT14, TDP1, SIL1, and POLG. This test in 2023 did not reveal any significant findings.

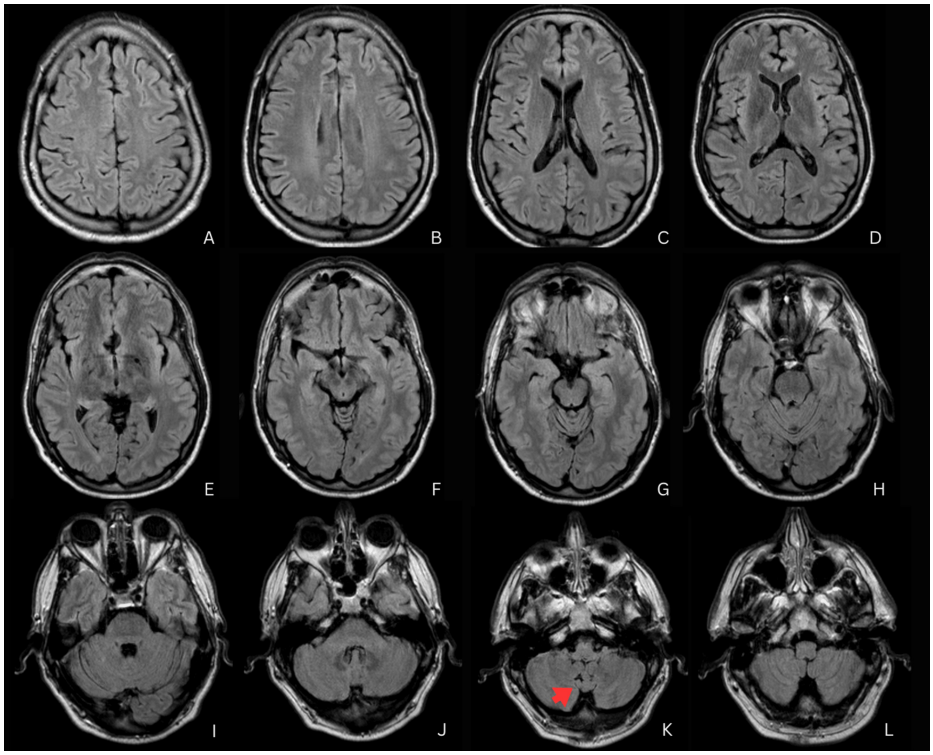


FIGURE 2: Axial fluid-attenuated inversion recovery (FLAIR) MRI sequences, in slices superior to inferior, revealing mild cerebellar atrophy, including the vermis, as shown by the red arrow in panel K.

A: Most superior slice of the brain, depicting the frontal and parietal lobes. B: Slightly inferior to the level of the slice shown in A, depicting the frontal and parietal lobes, as well as the beginnings of the lateral ventricles. C: Slightly inferior to the level of the slice shown in B, depicting the frontal and parietal lobes, as well as the insula and caudate head. D: Slightly inferior to the level of the slice shown in C, depicting the frontal and parietal lobes, as well as the insula, caudate head, and thalamus. E: Slightly inferior to the level of the slice shown in D, depicting the frontal, temporal, and occipital lobes, as well as the insula, thalamus, and lentiform nucleus. F: Slightly inferior to the level of the slice shown in E, depicting the frontal, temporal and occipital lobes, at the level of the rostral midbrain. G: Slightly inferior to the level of the slice shown in F, depicting the frontal, temporal and occipital lobes, at the level of the caudal midbrain. H: Slightly inferior to the level of the slice shown in G, depicting the temporal and occipital lobes at the level of the pons, with the anterior lobe of the cerebellum present. I: Slightly inferior to the level of the slice shown in H, depicting the temporal and occipital lobes at the level of the rostral pons and the fourth ventricle, with the posterior lobe of the cerebellum present. J: Slightly inferior to the level of the slice shown in I, depicting the temporal lobes at the level of the caudal pons, with the posterior lobe of the cerebellum present. K: Slightly inferior to the level of the slice shown in J, at the level of the caudal pons, with the posterior lobe of the cerebellum present, with mild cerebellar atrophy. L: Slightly inferior to the level of the slice shown in K, at the level of the medulla, with the posterior lobe of the cerebellum present.

His surgical history included removal of a kidney stone. His social history included occasional drinking and a 20-pack-year smoking history. He previously worked in roofing. He does not have any known drug allergies. The patient's medications included omeprazole for his GERD, as well as rosuvastatin and fenofibrate for his hypertriglyceridemia. The patient denied any exposure to dopamine blockers, significant exposure to pesticides, trichloroethylene, carbon disulfide, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and Agent Orange. The patient also denied recent travel outside of the country.

In the two years since his initial presentation, the patient developed emotional lability, episodes of suicidal ideation requiring hospitalization, urinary urgency and incontinence, ocular dysmetria, dysphagia, and tongue fasciculations. A trial of carbidopa-levodopa seemed to worsen his symptoms. At this time, laboratory testing for heavy metal poisoning, vitamin E and B12, paraneoplastic and autoimmune encephalitis, Lyme disease, and syphilis was unremarkable. An electroencephalogram (EEG) showed no epileptiform activity. A DaTscan demonstrated absent dopamine uptake in the left putamen and mildly decreased activity in the right putamen (Figure *3*). Repeat genetic testing with Varinatyx genomic unity whole-genome analysis revealed a pathologic F198S variant in the PRNP gene consistent with autosomal dominant GSS disease. As his symptoms progressed, he and his family decided to move the patient to an assisted living facility, where he receives physical and speech therapy. He also developed clinical depression and anxiety, which are managed medically.

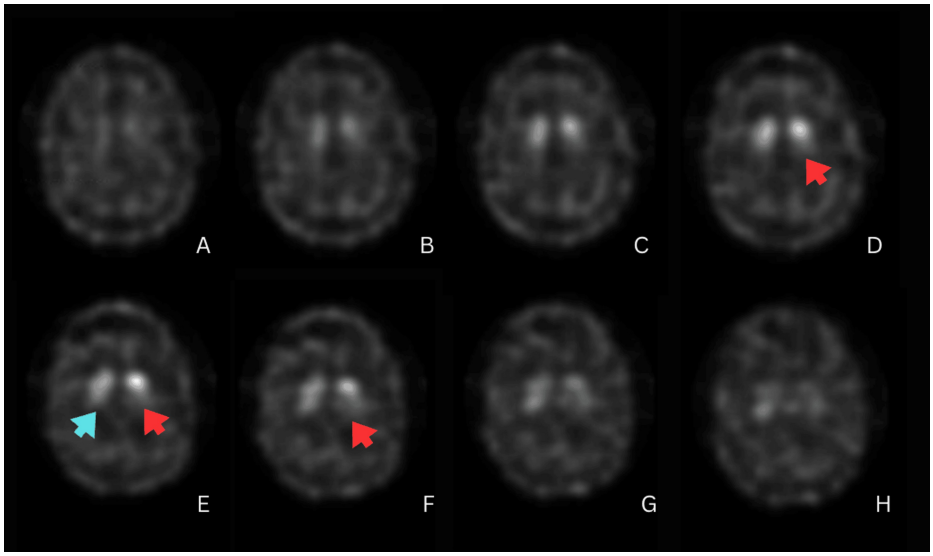


FIGURE 3: Patient dopamine transporter (DaT) Scan, with slides shown superior to inferior, with absent activity in the left putamen, as marked by the red arrows, and mildly decreased activity in the right putamen, as marked by the blue arrow.

A: Most superior slice, with putamen not yet visualized. B: Slightly inferior to panel A. C: Slightly inferior to panel B, with the putamen starting to be visualized. D: Slightly inferior to panel C, with the indicated left putamen showing less activity compared to the right. E: Slightly inferior to panel D, with the left putamen showing less activity as compared to the right. As indicated by the blue arrow, mildly decreased activity at the right putamen. F: Slightly inferior to panel E, with the indicated left putamen showing less activity compared to the right. G: Slightly inferior to panel F. H: Slightly inferior to panel G.

Discussion

GSS is a type of hereditary prion disease that affects approximately 12 per 100 million worldwide [7]. The F198S variant in this patient was inherited in an autosomal dominant fashion, but about one-third of cases are due to de novo mutations [9]. While this patient did follow the typical initial presentation of GSS with his ataxia and dysarthria, the initial differential included a hereditary cerebellar ataxia and atypical parkinsonisms. While MSA was the leading differential at the start of his workup, given his father's diagnosis, this patient did not have the autonomic dysfunction typical of MSA. At the time of this patient's father's diagnosis in 2006, whole-exome genetic testing was not available. The patient also did not completely fit the phenotype of progressive supranuclear palsy, given that he did not have difficulty with vertical eye movements. Since ataxia was one of his presenting symptoms, dementia with Lewy bodies was not as highly considered, as ataxia is not typically part of the symptom profile and his dementia developed later.

The patient's initial brain MRI showed mild cerebellar atrophy, which is not uncommon for GSS at the initial onset of symptoms [9]. A full workup for acquired ataxia was completed, with no positive findings at that time. The mutation affecting the presented patient was not included in the initial genetic testing provided by Athena. Given the lack of improvement with carbidopa-levodopa, further investigation was done, prompting the repeat genetic testing by a different genetic testing company with whole-exome sequencing revealing the GSS diagnosis. The patient's family history is consistent with autosomal dominant inheritance of GSS, and they were referred to genetic counseling.

Histopathologically, GSS has amyloid plaques made of prion protein that deposit in the cerebral and cerebellar cortex and the basal ganglia. The research on why there might be dopaminergic deficits in the striatum of patients with GSS is still in its infancy. There is only one other documented case with this particular variant having an abnormal DaTscan [5]. Our cases had similar presentations, sharing ataxia and cognitive impairment, as well as decreased uptake in the putamen on DaTscan. Our cases differ in responsiveness to carbidopa-levodopa. The patient in the cited case was initially positively responsive to carbidopa-levodopa, while the patient in our case worsened with the medication. Several reported cases of various variants of Creutzfeldt-Jakob disease (CJD) have had abnormal DaT scans, although not responsive to levodopa [5].

In 2024, a case series was published investigating five cases of reduced dopamine uptake in the striatum in patients with the P102L variant of GSS [1,6]. The authors describe that upon autopsy, there were prion

protein plaques and dopaminergic neuron loss in the substantia nigra of one patient with the P102L variant. Based on the analysis of those patient outcomes, they hypothesize that the prion proteins deposit in the presynaptic region of dopaminergic neurons in the striatum and cause nigrostriatal neurodegeneration [10].

There were a few limitations to our study. First, the patient did not have any UPDRS or cognitive testing scores completed at initial presentation. Moreover, while the patient did have a significant family history of symptoms similar to his, we were unable to collect firsthand patient history from them given they were no longer living.

Conclusions

We present a case of an F198S variant of GSS disease. While this patient followed the typical presentation of GSS, a family history of presumed MSA and negative initial genetic testing confounded the correct diagnosis initially. This case underscores the importance of completing and repeating genetic testing for patients who present with truncal ataxia and dysarthria, especially if the patient has a family history of parkinsonism.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Andrea Medina Garcia, Theresa A. Zesiewicz, Lindsey Evans

Acquisition, analysis, or interpretation of data: Andrea Medina Garcia, Theresa A. Zesiewicz, Lindsey Evans, Wendy Yang, Chase Kingsbury

Drafting of the manuscript: Andrea Medina Garcia, Theresa A. Zesiewicz, Wendy Yang, Chase Kingsbury

Critical review of the manuscript for important intellectual content: Andrea Medina Garcia, Theresa A. Zesiewicz, Lindsey Evans

Supervision: Theresa A. Zesiewicz, Lindsey Evans

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. University of South Florida Institutional Review Board issued approval STUDY009824. This study qualifies for a waiver of the requirement for signed authorization as outlined in the HIPAA Privacy Rule regulations at 45 CFR 164.512(i). **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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